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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/398,897	09/20/1999	RENJI YANG	0109015/016	1629

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EXAMINER
HAYES, ROBERT CLINTON

ART UNIT	PAPER NUMBER
1647	17

DATE MAILED: 11/19/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/398,897	Applicant(s) Yang et al
	Examiner Robert C. Hayes, Ph.D.	Art Unit 1647

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Sep 3, 2002* .

2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1, 4, 5, 12, 15, and 16* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *1, 4, 5, 12, 15, and 16* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 9/3/02 has been entered.

2. Applicant's arguments filed 09/03/02 have been fully considered but they are not deemed to be persuasive. It is noted that due to time constraints for the Office to move submitted responses, and Applicants' responsibility to follow up on any interview requests with the Examiner directly, the interview requested on page 5 of the response was not possible before first Office action.

3. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

4. Claims 1, 4-5, 12 & 15-16 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey

to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

No proper antecedent basis or conception exists on pages 1 or 3 for the broader concept for *neural precursor cells* maintaining "normal karyotypes and normal neuronal phenotypes *beyond thirty cell doublings*". In contrast, page 3 of the specification alternatively contemplates such for only "CNS stem cells"; thereby, constituting new matter.

5. Claims 1, 4-5, 12 & 15-16 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Nakafuka et al (IDS Ref #26), in view of Weiss et al. (U.S. Patent 5,851,832; IDS Ref #2), for the reasons made of record in Paper No.11 and as follows.

Applicants argue on page 6-8 of the response that the claims have been amended to recite "that the stable cell lines maintain normal karyotypes and normal neuronal phenotypes beyond thirty cell doublings". However, it remains reasonable the combined references' cells also "maintain normal karyotypes and normal neuronal phenotypes beyond thirty cell doublings", as recited in the claims; absent evidence to the contrary. Accordingly, it has been established by the courts that a product (i.e., as it relates to the required components in the currently claimed method) inherently possesses characteristics of that product (i.e., including that for the art recited neural precursor cell lines). See, e.g., *Ex parte Gray*, 10 USPQ2d, 1922; *In re Best*, 195 USPQ 430). In addition,

"the PTO can require an applicant to prove that the prior art products do not necessarily or inherently possess the characteristics of his claimed product. Accordingly, since the issue in the present appeal is whether the prior art factor is identified or patently indistinct from that of the material on appeal, appellants have the burden of showing that inherency is not involved". *Ex parte Gray,* 10 USPQ 2d 1922 (1989); *In re Best,* 195 USPQ 430 (CCPA 1976).

Lastly, it is noted that the courts have held that when the prior art product reasonably appears to be the same as that claimed (i.e., as it relates to the required components in the currently claimed method), but differs by process in which it is produced, a rejection of this nature is eminently fair and the burden is upon the appellants to prove, by comparative evidence, a patentable difference (*In re Brown*, 173 USPQ 685).

Therefore, Applicants' arguments remain not persuasive.

In summary, Nakafuka et al teach a method of producing stable mammalian neural precursor cells *in vitro* comprising preparing cultures of E12 embryonic rat neuroepithelial/neural precursor cells in Dulbecco's modified Eagle's medium with serum that reasonably contains mitogens, such as α FGF, bFGF, EGF and/or TGFα , followed by transfection with the same *mycer* construct as used in the instant application (i.e., c-myc cDNA construct fused to the ligand binding domain of an estrogen receptor; pg. 155 & 156; as it relates to claims 1a-c & 12a-c); thereby, establishing the clonal cell line, MNS-57. These MNS-57 cells were further cultured in the presence of a second mitogen, bFGF or EGF, in DF medium containing β-estradiol/ β-E2 (i.e., pgs. 155 & 157-159; Figs. 3 & 4; as it relates to claims 1d & 12d). However, Nakafuka et al. do not teach initial culturing of these neural precursor cells in medium that is serum-free, nor a method producing human neural precursor cells.

Weiss et al. teach that "a preferred embodiment for proliferation of neural stem cells is to use a defined serum-free culture medium, as serum tends to induce differentiation and contains unknown components" (col. 16, lines 23-26; as it relates to claims 1a & 12a). "The culture medium is supplemented with at least one proliferation-inducing growth factor" (col. 16, lines 41-42), in which "[p]referred proliferation-inducing growth factors include EGF and TGFα" (col. 16, lines 56-57; as it relates to claims 1b & 12b). Weiss also teach use of human pluripotent embryonic stem cells (cols. 13 & 15-16; as it relates to claims 4-5 & 15-16). However, Weiss et al. do not disclose transfection of neural precursor/stem cells with c-myc constructs fused to steroid/thyroid hormone receptor ligand binding domains to form stable cell lines.

It would have been obvious to one of ordinary skill in the art at the time of filing Applicants' invention to modify Nakafuka's method of producing mammalian neural precursor/stem cells by using serum-free medium and culturing neural precursor cells in the presence of the first mitogen, EGF or TGFα, as taught by Weiss, in order to prevent premature differentiation of these neural precursor cells (which include Weiss' human pluripotent embryonic stem cells; as it relates to claims 4-5 & 15-16) prior to being transfected with Nakafuka's c-myc construct fused with the ligand binding domain of an estrogen receptor, which results in immortalization of these cells. Nakafuka's step (d) can subsequently be carried out using the second mitogens, aFGF or bFGF, along with β-estrodiol/ β-E2, to more accurately

determine the effects of these defined components on the differentiation potential to neuronal-restricted cells, or alteratively to glial-restricted cells, etc.

6. Claims 1, 4-5, 12 & 15-16 are rejected under 35 U.S.C. 103(a) as being unpatentable over Nakafuka et al (IDS Ref #26), in view of Weiss et al. (U.S. Patent 5,851,832; IDS Ref #2) as applied to claims 1, 4-5, 12 & 15-16 above, and further in view of Eilers et al (IDS Ref #20) and/or Evans et al (1988), for the reasons made of record in Paper No.11 and as discussed above.

In summary, Nakafuka et al. and Weiss et al. are as described above. However, neither Nakafuka et al. nor Weiss et al. teach use of Nakafuka's c-myc constructs fused to other steroid/thyroid hormone receptor ligand binding domains.

Eilers et al. teach that a "similar chimaera, *mycgr*, that contains the sequence that encodes the hormone [ligand] -binding domain of the rat glucocorticoid receptor fused to the 3' end of *myc* transforms these cells in a glucocorticoid-dependent manner (pg. 67, 1st *pp*; as it relates to claims 1 & 12).

Evans is a review describing the well known ligand binding domains of steroid/thyroid hormone receptors (e.g., pg. 891; as it relates to estrogen, androgen, progesterone, glucocorticoid, thyroid hormone, retinoid and ecdysone receptors and their respective ligands/myc-activating chemicals in claims 1c-d & 12c-d).

It would have been obvious to one of ordinary skill in the art to produce stable mammalian/human neural precursor cells using the method of Nakafuka et al. in view of Weiss

et al. modified using any well known steroid/thyroid hormone receptor ligand binding domain fused to Eilers' c-myc constructs, because Eilers et al teach that "similar chimaeras" transform cells in a steroid/thyroid hormone-dependent manner.

7. Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner Robert Hayes whose telephone number is (703) 305-3132. The examiner can normally be reached on Monday through Friday from 8:30 AM to 5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Kunz, can be reached on (703) 308-4623. The fax phone number for this Group is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Robert C. Hayes, Ph.D.
November 15, 2002

GARY KUNZ
SUPERVISORY PATENT EXAMINER
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